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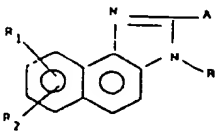
(54) **New 3H-naphtho(1,2-d)imidazoles, processes for preparing them, their use as antiinflammatory and antimicrobial agents and compositions containing them.**

(57) 3H-naphth[1,2,-d] imidazole derivates of formula



wherein R stands for (C_{1-6})alkyl, (C_{3-6})alkenyl, (C_{3-6}) alkynyl or (C_{3-7})cycloalkyl, R_1 and R_2, each independently may represent hydrogen, halogen, (C_{1-4})alkyl, (C_{1-4})alkylthio, (C_{1-4})alkoxy or halo(C_{1-4})alkoxy and the symbol A represents a 5- or 6-membered heteroaromatic ring or a phenyl radical optionally substituted, are claimed.

Also described and claimed are processes for preparing the novel compounds, their use as antiinflammatory and antimicrobial agents and pharmaceutical compositions containing them.

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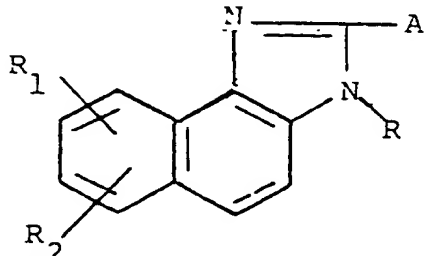
NEW 3H-NAPHTHO[1,2-d]IMIDAZOLES, PROCESSES FOR PREPARING THEM, THEIR USE AS ANTIINFLAMMATORY AND ANTIMICROBIAL AGENTS AND COMPOSITIONS CONTAINING THEM.

The present invention relates to novel 3H-naphto[1,2-d] imidazole derivatives of the following general formula I



I

wherein R stands for (C_{1-6})alkyl, (C_{3-6})alkenyl, (C_{3-6})alkynyl or (C_{3-7})cycloalkyl, R_1 and R_2, each independently may represent hydrogen, halogen, (C_{1-4})alkyl, (C_{1-4})alkylthio, (C_{1-4})alkoxy or halo(C_{1-4})alkoxy and the symbol A represents a 5- or 6-membered heteroaromatic ring which may contain one or two heteroatoms independently selected from oxygen, nitrogen and sulfur and may be optionally substituted with (C_{1-4})alkyl or phenyl groups, or it may represent a phenyl radical optionally substituted with one to three groups independently selected from halogen, (C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{3-4})alkenyloxy, (C_{3-4})alkynyloxy, hydroxy, benzyloxy, (C_{2-4})alkanoyloxy, carboxymethoxy, [carbo(C_{1-4})alkoxy]methoxy, methylenedioxy, amino, mono- and di-(C_{1-4})alkylamino, (C_{2-4})alkanoylamino, benzoylamino and a heterocyclic radical derived from pyrrolidine, piperidine, piperazine, (C_{1-4})alkyl piperazine and morpholine; with the proviso that when R

represents a methyl group and R_1 and R_2 are both hydrogen, A can not represent a 2-hydroxyphenyl group, and with the further proviso that when simultaneously R stands for an ethyl radical, one of R_1 and R_2 is hydrogen and the other is a methoxy group, A cannot be a 4-dimethylaminophenyl group; and salts therewith of pharmaceutically acceptable acids.

The novel compounds of the present invention possess antiinflammatory, analgesic, antipyretic and antimicrobial utility.

The compounds excluded from the present invention by the above provisos are known from German Patent No. 1.137.625 which reports several thiazole, oxazole and imidazole derivatives with photoconductive properties, that can suitably be employed for electrophotographic reproduction.

A compound as in formula I but wherein R is methyl, R_1 and R_2 are hydrogen and A means a nitro-substituted phenyl group, is known from the article by J.W. Lown and M.H. Akhtor published in Can.J. Chem. 49, (1971) 1610, where the authors discuss the mechanisms involved in the reaction of 1-nitroso-2-naphthylamine with 3-aroyl-aziridines.

Moreover, other naphthoimidazoles, substituted in the 2-position by an alkyl group, are described in U.S. Patent No. 3,046,116 where it is said that these compounds can be conveniently used in the production of printing plates.

As used herein the term "(C_{1-4})alkyl" and the alkyl portion of other hereinlisted radicals containing a (C_{1-4})alkyl moiety identifies a straight or branched alkyl radical having from 1 to 4 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl and 1,1-dimethylethyl while the term "(C_{1-6})alkyl" designates a straight or branched alkyl radical containing up to 6 carbon atoms such as those listed before, pentyl, 1-ethylpropyl, 1-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, hexyl, 1-methylpentyl, 4-methylpentyl, 1,3-dimethylbutyl, 3,3-dimethylbutyl and the like. The expression "(C_{3-6})alkenyl" identifies straight or branched alkenyl groups containing 3 to 6 carbon atoms and one or two double bonds, such as, 2-propenyl, 1-methyl-2-propenyl, 2-butenyl, 1-methyl-2-butenyl, 2,4-hexadienyl, 1-methyl-2,4-pentadienyl and the like. The term "(C_{3-6})alkynyl" designates straight or branched alkynyl groups containing 3 to 6 carbon atoms and one or two triple bonds, such as, 2-propynyl, 1-methyl-2-propynyl, 2-butynyl, 1-methyl-2-butynyl, 2,4-hexadiynyl and the like. The term "(C_{3-7})cycloalkyl" indicates cycloalkyl radicals of 3 to 7 carbon atoms selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The expression "(C_{1-4})alkoxy" identifies straight or branched alkoxy radicals having at most 4 carbon atoms which are selected from methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy, 1,1-dimethyletoxy; and the terms "(C_{3-4})al-

kenyloxy" and "(C_{3-4})alkynyloxy" designate branched or linear 3 or 4 carbon atoms alkenyloxy and alkynyloxy groups such as 2-propenyloxy, 1-methyl-2-propenyloxy, 2-methyl-2-propenylxoy, 2-butenyloxy and 2-propynyloxy, 1-methyl-2-propynyloxy and 2-butynyloxy respectively. The term and the moiety halogen essentially identifies chloro, bromo and fluoro. The expression "5 or 6 membered heteroaromatic ring" means a heterocyclic ring of 5 or 6 atoms which has a certain degree of aromatic character. Are therefore included in this definition the following radicals: thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimydyl, pyridazinyl, isothiazolyl, isoxazolyl, furazanyl, triazolyl, and the like.

A preferred group of compounds comprises those compounds of formula I wherein R stands for (C_{1-6})alkyl, (C_{3-6})alkenyl, (C_{3-6})alkynyl or (C_{3-7})cycloalkyl, R_1 and R_2 each independently represent hydrogen, halogen or (C_{1-4})alkoxy and the symbol A represents a phenyl radical optionally substituted with one to three groups independently selected from halogen, (C_{1-4})alkyl, (C_{1-4})alkoxy, hydroxy, benzyloxy, (C_{2-4})alkanoyloxy, carboxy-methoxy, /carbo(C_{1-4})alkoxy/methoxy, methylenedioxy, amino, mono- and di-(C_{1-4})alkylamino, (C_{2-4})alkanoylamino and benzoylamino; with the proviso that when R represents methyl and R_1 and R_2 are both hydrogen, A can not represent a 2-hydroxyphenyl group, and with the further proviso that when simultaneously R stands for ethyl, one of R_1 and R_2 is hydrogen and the other is a methoxy group, A cannot re-

present a 4-dimethylaminophenyl group; and salts therewith of pharmaceutically acids.

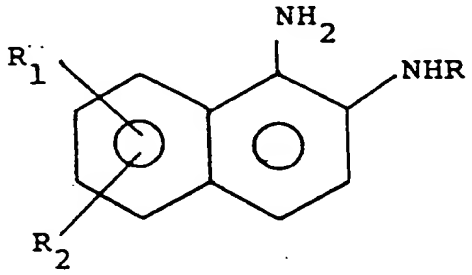
A second preferred group of compounds comprises those compounds of formula I wherein R stands for (C_{1-6})alkyl, R_1 and R_2 are hydrogen and the symbol A represents a heteroaromatic ring selected from furyl, thienyl, pyridyl and pyrrolyl, optionally substituted by (C_{1-4})alkyl groups; and salts therewith of pharmaceutically acceptable acids.

A most preferred group comprises those compounds of formula I wherein R stands for (C_{1-6})alkyl, R_1 and R_2 are both hydrogen and the symbol A represents a phenyl radical optionally substituted with one to three groups independently selected from (C_{1-4})alkyl, (C_{1-4})alkoxy, amino, mono- and di-(C_{1-4})alkylamino;and salts therewith of pharmaceutically acceptable acids.

These acid addition salts are obtained by treating compounds of formula I above with pharmaceutically acceptable acids. As acids suitable for the formation of therapeutically acceptable salts there may be mentioned, for example, hydrohalide, sulfuric and phosphoric acids, nitric and perchloric acids; aliphatic, alicyclic, aromatic or heterocyclic carboxylic or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, pyruvic acid; phenylacetic, benzoic, para-aminobenzoic, anthranilic, para-hydroxybenzoic, salicylic, para-aminosalicylic or embonic acid, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic acid; halobenzensulfonic, toluenesulfonic, naphthalenesulfonic acids or sulfanilic acid.

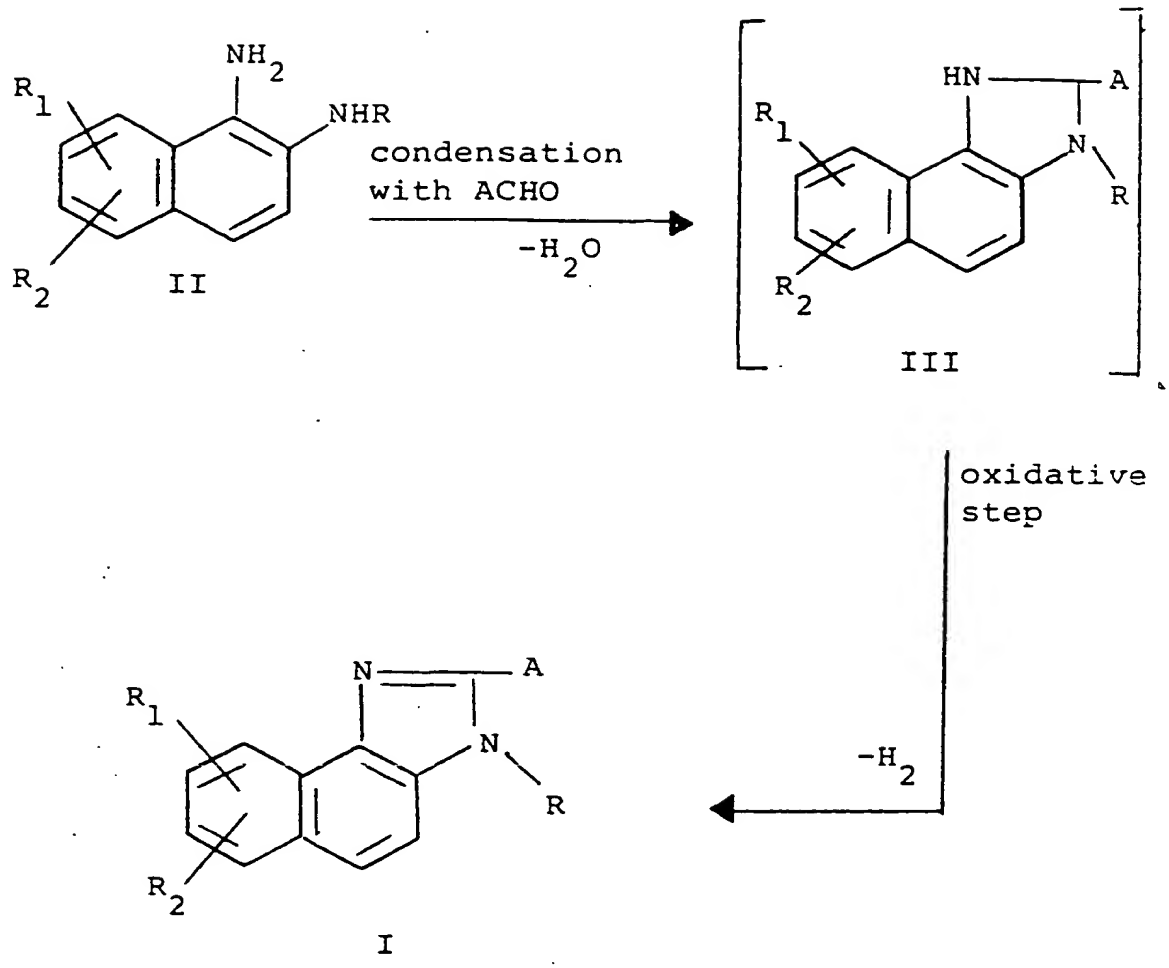
These or other salts of the new compounds may also be used for purifying the resulting compounds by converting them into salts, isolating the latter and liberating the free compound from them. In view of the close relationship between the new compounds in the free form and in the form of their salts what has been said above and hereinafter with reference to the free compounds concerns also the corresponding salts.

A general method for preparing the novel compounds comprises the condensation between a naphthalenediamine of formula II



II

wherein R, R_1 and R_2 are as defined before, and a suitably selected aldehyde of formula ACHO, wherein A is as defined before, to yield an intermediate imidazoline which is subsequently oxidized to end product I. The overall reaction is better illustrated in the following scheme A



wherein the square brackets mean that the intermediate compound placed within them can be further processed without previous separation.

Widely varying conditions can be used to bring about the condensation between the naphthalenediamine and the aldehyde; however rather good results have been obtained adding an equimolecular proportion or a slight excess of the aldehyde to a solution of the compound of formula II in an inert high boiling organic solvent such as for

instance xylene, toluene, or cymene and then refluxing the obtained reaction mixture in a Dean-Stark apparatus under inert atmosphere.

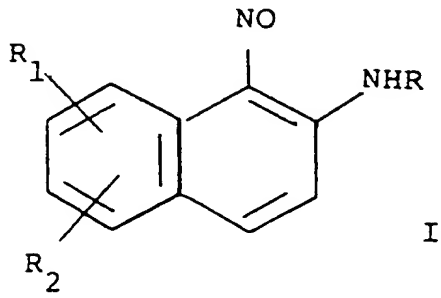
As for the oxidative step which in the above scheme is visualized as a simple dehydrogenation, it can be performed in the presence of a mild oxidizing agent, such as for instance manganese dioxide or cupric acetate, or better with a dehydrogenating agent suitably selected from the group of metals or metal oxides generally employed and named as "hydrogenating catalysts" such as for instance Palladium, Platinum, Ruthenium, Rhodium, Platinum dioxide, either in powder form or adsorbed on a charcoal or asbestos carrier, and Raney-Nickel. The obtained reaction products are recovered by conventional procedures which involve filtration of the hot solution and evaporation of the solvent under reduced pressure. Purification of the raw material thus obtained is achieved simply by crystallization or by means of chromatographic techniques.

The starting naphthalenediamine derivatives of formula II are generally novel and may be prepared through different routes; for instance, in J. Org. Chem. 37 (22), 3566 (1972), the synthesys of N^2-isopropyl-naphthalen-1,2-diamine is reported through a) nitration of β-naphthaleneamine to 1-nitro-2-naphthaleneamine, b) exchange of the amino group with a chlorine atom, c) amination with isopropylamine and finally d) reduction of the nitro group to amino.

Other methods moreover can be gathered from the literature considering the particular reactivity of the naphthalene substratum.

The process we have generally employed for preparing the starting naphthalenediamine derivatives involves the re-

duction of a N-substituted-1-nitroso-2-naphthaleneamine of formula



IV

wherein R, R_1 and R_2 are as defined before, by means of hydrogen gas in the presence of a hydrogenating catalyst. Various hydrogenation catalysts may be employed to bring out the conversion to diamines and generally the same metals and metal oxides employed in the oxidative step of scheme A are preferably used, i.e. Palladium, Platinum, Ruthenium, Rhodium, Platinum dioxide, either in powder form or adsorbed on a carrier, and Raney-nickel. Also the reaction conditions may vary widely since all the catalysts listed above are active, and are preferably used, at room temperature and atmospheric pressure but can suitably be employed also up to 4 atmospheres. Solvents which can conveniently be employed in this reaction are selected from lower aliphatic alcohols such as methanol and ethanol and aromatic hydrocarbons such as for instance benzene, toluene, xylene and cymene.

Alternatively reduction of the N-substituted-1-nitroso-2--naphthalenamine derivative can also be accomplished by using as reducing agents metals such as tin, zinc or aluminum in an acidic medium according to well known procedures.

The starting nitroso compounds have been synthetized according to the method described by S.T. Morgan and F.P. Evens in J. Chem. Soc. 115, 1140 (1919), through acid-catalyzed rearrangement of a 2-(N-nitroso-N-substituted)naphthylamine or more conveniently through reaction of primary amines with 1-nitroso-2-naphthol according to E.W. Malmberg and C.S. Hamilton in J. Am. Chem. Soc. 70, 2415 (1948).

The above reported method for preparing the starting naphtalenediamines II from the corresponding N-substituted-1-nitroso-2-naphthaleneamines is of particular value for many reasons. First of all in fact the reduction reaction does not require drastic conditions but on the contrary it proceeds rapidly at room temperature and atmospheric pressure, secondly the reaction conditions themselves, the solvents and the starting nitroso-compounds employed are particularly safe from the industrial point of view; thirdly the naphthalenediamines thus obtained are not necessarily separated from the reaction mixture and the condensation with the suitably selected aldehyde ACHO can be carried out without any working up of the reaction mixture containing the hydrogenated compound of formula II before adding the aldehyde ACHO. In this case, if separation of the naphthalenediamines is not required, also the reduction of the N-substituted-1-nitroso-2-naphthaleneamines will be carried out in an inert high-boiling organic solvent.

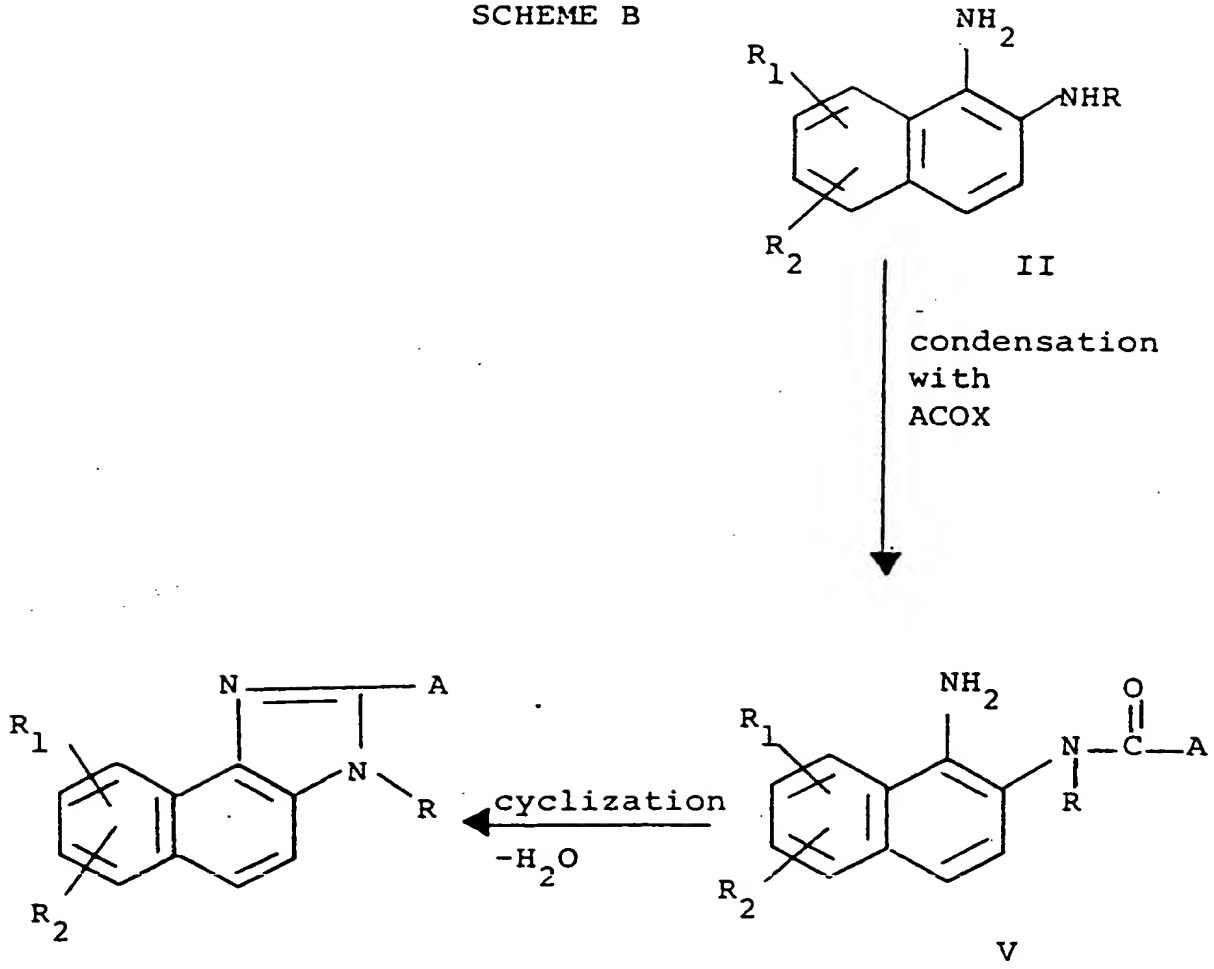
Moreover, since catalyzed reduction, which takes place on the catalyst's surface, is a reversible process, the same catalysts employed for reducing the nitrosonaphthaleneamines can be conveniently employed in the absence of hydrogen, in the dehydrogenation procedure.

The interaction between a naphthalenediamine of formula II and an acid derivative which may be an acyl chloride, anhydride or ester provides an other convenient route to the naphthoimidazoles of the present invention. More particularly, the naphthalenediamine is contacted with a compound of formula ACOX wherein A is as defined before and X may represent

- a chlorine atom,
- a group $-OR_3$ wherein R_3 may be the same radical -COA, or a trifluoroacetyl, ethoxycarbonyl or alkyl sulfonyl moiety or,
- a group $-OR_4$ wherein R_4 is a methyl or ethyl radical.

This two step reaction involves formation of a mono-acylated naphthalenediamine as the key intermediate according to the following scheme B:

SCHEME B



As for the first step which leads to the intermediate mono-acylated compounds, we found that high yields can be realized when an equimolecular mixture of a naphthalendiamine II and an acid derivative ACOX is dissolved in an anhydrous inert organic solvent selected from lower aliphatic halogenated and aromatic hydrocarbons in the presence of a tertiary organic nitrogen base which should block the inorganic or organic acid which forms during the course of the reaction.

Finally, conversion of the mono-acylated intermediate to the desired end product, through elimination of water, is carried out by refluxing it in an inert organic solvent optionally in the presence of an acidic catalyst such as sulphuric or p-toluenesulphonic acid. Recovery and purification of the end naphthoimidazoles, involves the same conventional procedures already described in the first process. Furthermore some compounds of formula I may be obtained also through chemical modifications of other compounds, falling within the same formula I, prepared according to one of the reaction schemes outlined before. For instance, compounds wherein A is phenyl substituted with (C_{1-4})alkoxy, (C_{3-4})alkenyloxy, (C_{3-4})alkynyloxy, benzyloxy, (C_{2-4})alkanoyloxy, carboxymethoxy, or /carbo(C_{1-4})alkoxy/methoxy are conveniently prepared by reaction of the corresponding hydroxyphenyl derivatives with suitable agents such as (C_{1-4})alkyl-, (C_{3-4})alkenyl-, (C_{3-4})alkynyl- and benzyl halogenides, tosylates or mesylates, (C_{2-4})alkanoyl halogenides or anhydrides, an α-haloacetic acid and its (C_{1-4})alkyl esters. Again, the compounds wherein A is an aminophenyl group may be easily prepared from the corresponding alkanoylamino and benzoylaminophenyl derivatives by acid hydrolysis. A convenient route leading to monoalkylaminophenyl compounds in high yields, consists in preparing the sodium derivative of the amidic nitrogen atom of a corresponding acylamino derivative, then substituting it by means of an alkylating agent and finally splitting off the protecting acyl group by alkaline hydrolysis.

It is intended that alternative methods which can suitably be employed for transforming a pre-existing radical into another falling within the given meanings, although not specifically disclosed, are to be considered within the scope of the present invention.

As stated before, some of the novel compounds of the present invention are active as antiinflammatories, mild analgesics and antipyretics. Moreover, some others possess a fairly good antimicrobial activity particularly against fungi. These biological activities are coupled with a low toxicity since the approximate LD_{50}s per os in mice are generally higher than 500 mg/kg. The toxicities were determined according to Lichtfield and Wilcoxon, Journ. Pharm. Expt. Ther., 96, 99, (1949).

The antiinflammatory activity was ascertained by means of several testing methods; in one, the ability of the compounds of the invention to reduce the edema induced in the rat paw by injection of carrageenin was evaluated and the test was performed according to the methodology described by C.A. Winter et al. in Proc. Soc. Exptl. Biol. Med. 111, 544, (1962).

In another it was investigated the reduction by the test compounds of the weight of the granuloma formed on a cotton pellet implanted subcutaneously in rats, following the method described by Meier et al. in Experimentia, 6, 469, (1950).

In still another some of the compounds were tested in the adjuvant induced arthritis test in rats.

This test which was performed as described by B.B. Newbould in Bri. Journ. Pharmacol., 21, 127,(1963), is absolutely meaningful, because adjuvant arthritis is one of the best pharmacological tool with which a pharmacologist can investigate compounds as to their possible antiinflammatory activity, owing to the fact that this experimental model of chronic inflammation looks closer like to the conditions of the rheumatoid arthritis of the human pathology (see Pearson, C.M., Arthritis and allied conditions, page 119, Lea and Febiger Publ. 1967 and Pearson C.M., J. Chronic Diseases, 16, 863 (1963). The compounds were administered to the rats at different dose levels generally corresponding to about one twentieth or one twentyfifth, one tenth and one fifth (the highest dose) of the corresponding toxic doses expressed in LD_{50} values. However, even if the LD_{50} values of the compounds to be tested are higher than 1000 mg/kg, the maximum dose level at which they are administered is generally never higher than 200 mg/kg. These dosages are quite far from the toxic dose. Actually, in the carrageenin-induced oedema test, used as a preliminary screening test, the compounds to be tested were first administered at the highest dose level which, as stated above, corresponds to one fifth of the LD_{50} value or 200 mg/kg if the LD_{50} value is higher than 1000mg/kg. The compounds displaying an interesting degree of antiinflammatory activity i.e. those causing a percent decrease of the induced edema of about 40 or more, were further tested at lower dosages and then submitted to the granuloma pellet test. The results obtained in these tests are reported in the following Table I:

TABLE I

Compound of Example No.	LD_{50} os	Dose mg/kg os	Percent inhibition of the carrageenin-induced edema	Percent inhibition of the granuloma pellet
1	1000	50	24	-
		100	37	-
		200	42	24
4	1000	50	30	-
		100	44	-
		200	63	33
5	> 1000	50	21	
		100	37	-
		200	45	40
6	~ 1000	50	34	-
		100	41	-
		100	53	40
13	> 1000	50	19	-
		100	31	-
		200	40	31

Compound of Example No.	LD_{50} os	Dose mg/kg os	Percent inhibition of the carrageenin-induced edema	Percent inhibition of the granuloma pellet
14	500	20	32	-
		50	46	-
		100	54	24
19	500	20	35	-
		50	50	-
		100	64	38
23	500	20	29	-
		50	37	-
		100	47	33
32	> 1000	50	32	-
		100	45	-
		200	48	45
38	> 1000	20	31	-
		50	45	-
		100	49	-
		200	52	31

The compounds of examples 6, 19 and 32 which gave the best results in the carrageenin-induced edema and in the granuloma pellet tests, were then further tested in the adjuvant arthritis test at a dosage corresponding to 1/5 of their LD_{50} or at 200 mg/kg if the LD_{50} is higher than 1000. The measure of effectiveness of the compounds in this test is given by their ability in reducing the volume of the hind paws of the rats. The results obtained are collected in Table II below:

TABLE II

Compound of Example No.	Dose mg/kg rats p.o.	%Reduction of the volume of the hind paws over the control
6	200	33
19	100	42
32	200	53

These favorable characteristics are coupled also with interesting analgesic and antipyretic properties which were investigated according to the methods described by Randall et al. in Arch. Int. Pharmacodyn. 111, 409, (1957) and by Buller et al. in J. Pharm. Pharmacol. 9, 128, (1957) respectively. It is finally to be noted that the new naphthoimidazoles which are the object of the present invention display a very low ulcerogenic activity which is several times lesser than the one observed with other known and therapeutically used antiinflammatory substances. The ulcerogenic action was determined according to Thuillier et al. Chim. Ther. 3, 51, (1968).

Moreover, as anticipated, some of the compounds of the present invention show an appreciable antimicrobial effect mainly against fungi such as various Trichophyton species, for instance Trichophyton mentagrophytes, Trychophyton Schoenleinii and Trichophyton versicolor. More particularly, concentrations varying from about 3 to about 25 γ/ml of the compounds of Examples 6, 11, 13, 15, 16, 17 and 18 inhibit the growth of these microorganisms in vitro.

The use of the novel compounds as antiinflammatory and as antimicrobial agents, which is a further specific object of the present invention refers to all industrially applicable aspects and acts of said use including the embodying of the novel compounds or their salts into pharmaceutical compositions.

For antiinflammatory use the compounds of the invention may be administered by different routes. While the preferred routes of administration are oral and rectal, parenteral administration can also be employed. For oral administration the compounds of the present invention are compounded into pharmaceutical dosage forms such as for instance tablets, capsules, elixirs, solutions and the like. Tablets may contain in addition to the therapeutic ingredient the usual additives such inert diluents, for example starch, lactose, kaolin, calcium phosphate, mannitol and the like; binders, for example gelatin, starch, sugars, gums, carboxymethylcellulose, polyvinylpyrrolidone, and the like; lubricants, for example talc, magnesium stearate, stearic acid and the like; and the commonly employed

disintegrant, coloring, sweetening and flavoring agents. Coated or hard-shell capsules may also be prepared which may contain the same additives indicated above for tablets.

Liquid preparations such as elixirs and solutions are prepared by dissolving the active ingredient in an aqueous or non-aqueous pharmaceutically acceptable solvent and may contain also suspending sweetening, flavoring and preservative agents as known in the art.

For rectal administration the compounds are formulated as suppositories wherein the active ingredient is admixed with convéntional vehicles such as for example cocoa butter, wax, spermaceti or polyoxyethylenglycols and their derivatives.

The dosage range is from about 0.05 to about 10.0 g. per day, preferably administered in divided doses. Accordingly, the present invention provides a pharmaceutical composition for antiinflammtory use comprising from about 50 to about 1000 mg of a compound of the invention as the active ingredient together with a pharmaceutically acceptable carrier.

For antimicrobial use the compounds of the invention are compounded into topical preparations such as ointments, creams, powders and the like in concentration of 0.1 to 10% to be applied one or more times a day as required. Ointments and creams are prepared by incorporating the active ingredient into an ointment base such as for instance a oleaginous base prepared from vegetable and animal fats, a hydrocarbon base prepared from petrolatum and wax or, preferably a polyethylenglycol ointment base.

Powders are prepared by mixing the active ingredient in the form of a very finely suddivided powder with a chemically inert vehicle as known in the art.

The following examples illustrate the process of the invention and describe in detail some compounds of general formula I without limiting the scope of the invention.

Example 1: 3-methyl-2-phenyl-3H-naphtho/1,2-d/imidazole

11.35 g of benzoyl chloride (0.08 mole) dissolved in 50 cc of methylene chloride is added to a solution of 14.57 g of N^2-methylnaphthalene-1,2-diamine (0.084 mole) and 11.3 cc of triethylamine (0.08 mole) in 100 cc of methylene chloride, and the obtained reaction mixture is allowed to stand at room temperature for about one hour. Then it is heated to the reflux temperature for 16 hours, cooled to room temperature and filtered over bleaching earth. The filtrate is diluted with 200 cc of methylene chloride, washed twice with water, once with 5% sodium bicarbonate and then with water up to neutral reaction of the aqueous phase. The methylene chloride solution, dried over sodium sulphate, is concentrated to dryness yielding a residue which taken up with 300 cc of benzene is then poured into a 500 cc flask equipped with a Dean Stark apparatus. 0.18 g of p-toluensulphonic acid is gradually added to this solution heated to the reflux temperature.

After 4 hours, the reaction mixture is cooled to room temperature and filtered. The filtrate washed with water, is dried over sodium sulphate and then concentrated to dryness yielding 13.1 g of the compound of the title. M.p. 127-28°C (from ethanol).

Example 2: 2-(4-chlorophenyl)-3-methyl-3H-naphtho[1,2-d]imidazole

The compound of the title is prepared essentially by following the procedures of the foregoing example but using 4-chlorobenzoyl chloride (14.15 g) instead of benzoyl chloride. Yield 16.47 g of pure compound. M.p. 152-153°C (from ethanol).

Example 3: 2-(3-methoxyphenyl)-3-methyl-3H-naphtho[1,2-d]imidazole

This compound is prepared according to the procedures of example 1 but using 3-methoxybenzoyl chloride (13.75 g) instead of benzoyl chloride. Yield 12.57 g. M.p. 148-149°C (from ethanol).

Example 4: 3-methyl-2-(4-pyridyl)-3H-naphtho[1,2-d]imidazole

The compound of the title is prepared by operating according to the procedures of example 1 but using isonicotinoyl chloride hydrochloride (14.25 g) instead of benzoyl chloride.

Yield 5.72 g of pure compound. M.p. 158-159°C (from ethanol).

Example 5: 3-methyl-2-(4-ethoxyphenyl)-3H-naphtho[1,2-d]imidazole

A solution of 11.16 g (0.06 mole) of 2-methylamino-1-nitrosonaphthalene in 800 cc of toluene is hydrogenated at room temperature and at the atmospheric pressure in the presence of 3 g of Palladium-on-carbon. After one hour, when the theoretical amount of hydrogen has been consumed, 9 cc (0.06 mole) of 4-ethoxy benzaldehyde are added and the obtained reaction mixture is heated to the reflux temperature under an inert atmosphere for about 3 hours. The water which forms during the reaction distillates as binary azeotrope with toluene and is separated through a Dean-Stark apparatus. Then further 1.5 g of 5% Palladium-on-carbon are added and reflux is prolonged for two additional hours. Filtration of the hot solution followed by concentration of the filtrate to dryness under vacuum affords a residue which has been purified by cristallization from ethyl acetate. Yield 14.5 g (80%) M.p. 138-9°C.

Examples 6 to 21

The following compounds are prepared by operating according to the procedures of the foregoing example, by hydrogenating the starting N-methyl-1-nitroso-naphthalenamine, condensing the obtained diamino compound with a suitable

selected aldehyde and then dehydrogenating the resulting imidazoline derivative.

6) 2-(4-methoxyphenyl)-3-methyl-3H-naphtho[1,2-d]imidazole M.p. 132-134 ^{0}C (from ethyl acetate)

7) 2-(3-chlorophenyl)-3-methyl-3H-naphtho[1,2-d]imidazole M.p. 137-9 ^{0}C (ethyl acetate)

8) 3-methyl-2-(2-pyridyl)-3H-naphtho[1,2-d]imidazole hydrochloride M.p. 231 ^{0}C (with decomposition) (from ethyl acetate).

9) 3-methyl-2-(6-methyl-2-pyridyl)-3H-naphtho[1,2-d]imidazole hydrochloride. M.p. 262 ^{0}C (decomposition) (from ethanol)

10) 3-methyl-2-(3-pyridyl) 3H-naphtho[1,2-d]imidazole hydrochloride. M.p. 245 ^{0}C (decomposition) (from methanol).

11) 2-(2-furanyl)-3-methyl-3H-naphtho[1,2-d]imidazole hydrochloride. M.p. 243 ^{0}C (decomposition) (from isopropanol).

12) 3-methyl-2-(1H-pyrrol-2-yl)-3H-naphtho[1,2-d]imidazole. M.p. 283 ^{0}C (from dioxane)

13) 3-methyl-2-(2-thienyl)-3H-naphtho[1,2-d]imidazole M.p. 166-8 ^{0}C (from ethyl acetate)

14) N,N-dimethyl-4-(3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)benzenamine. M.p. 136-8 ^{0}C (from benzene)

15) 3-methyl-2-[4-(1-methylethoxy)phenyl]-3H-naphtho[1,2-d]imidazole. M.p. 144-45 ^{0}C (from ethyl ether).

16) 3-methyl-2-(4-methylphenyl)-3H-naphtho[1,2-d]imidazole. M.p. 135-6 °C (from diisopropyl ether)

17) N,N-diethyl-4-(3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)benzenamine. M.p. 161-162,5 °C (from ethyl acetate)

18) 2-(1,3-benzodioxol-5-yl)-3-methyl-3H-naphtho[1,2-d]imidazole. M.p. 200-201 °C (from acetone)

19) 4-(3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)-2,N,N-trimethylbenzenamine. M.p. 116-118 °C (from methyl-t.butyl ether)

20) 3-methyl-2-(3-methyl-4-methoxyphenyl)-3H-naphtho[1,2-d]imidazole. M.p. 104-105 °C (from diisopropyl ether).

21) N-[4-(3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)phenyl]acetamide. M.p. 271-72 °C (from ethanol).

Example 22: 4-(3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)-benzeneamine

The compound of the title is prepared by acid hydrolysis of the corresponding monoacetyl derivative. More particularly a solution of 5.7 g of the compound of example 21 in 75 cc of 5% HCl is heated to the reflux temperature for about $1\frac{1}{2}$ hours under a nitrogen stream. Then the solution is treated with charcoal and filtered under vacuum. The filtrate brought to basic pH by treating with concentrated ammonium hydroxide, is then cooled and the solid which precipitates is recovered by filtration. M.p. 250-2 °C.

Example 23: N-methyl-4-(3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)benzeneamine

5 g of N-[4-(3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)phenyl]acetamide prepared as in Example 21 are dissolved in 80 cc of anhydrous dimethylformamide and to the obtained solution, cooled to a temperature comprised between 0^0 and 5^0C, 0.69 g of 55% NaH are gradually added. After $1\frac{1}{2}$ hours when the evolution of hydrogen gas ceases 1 cc of methyl jodide dissolved in 20 cc of dimethylformamide is dripped in and the reaction mixture is allow to reach room temperature. Then the solution is poured into 1 lt. of water and stirred for about 20 minutes; the solid which precipitates is recovered by filtration and dried under vacuum yielding 4.53 g of a mixture of two products one of which does correspond to the desacetylated product. This mixture is dissolved in 300 cc of methyl alcohol and 200 cc of 10% NaOH and refluxed for 6 hours; then methanol is distilled off at atmospheric pressure and the reaction mixture is cooled and diluted with water. The precipitate which forms is recovered by filtration and crystallized from benzene yielding 3.6 g of the compound of the title which melts at 225-27^0C.

Example 24: 4-(3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)phenol

This compound is prepared according to the procedures described under Example 5 but using 4-hydroxy-benzaldehyde instead of 4-ethoxybenzaldehyde. M.p. > 300^0C (from acetic acid).

Example 25: 3-methyl-2-/4-(phenylmethoxy)phenyl/-3H-naphtho/1,2-d/imidazole

2.47 g of 4-(3-methyl-3H-naphtho/1,2-d/imidazol-2-yl)phenol of the preceding example, 3.79 g of benzyl chloride, 3.11 g of tributylbenzyl ammonium chloride, 150 cc of methylene chloride and 15 cc of 1N NaOH are poured into a 500 cc flask and vigorously stirred at room temperature for about 6 hours. After this time the organic layer is separated, washed with 5% NaOH and with water and dried over Magnesium Sulfate. Evaporation of the solvent affords a raw residue which purified by column chromatography (cyclohexane:ethyl acetate 7:3) yields 2.21 g (69%) of the compound of the title. M.p. 148-49^{0}C (from ethanol).

Example 26: 4-(3-methyl-3H-naphtho/1,2-d/imidazol-2-yl)phenol acetate

A solution of 5.48 g (0.02 mole) of the compound of example 24 in 100 cc of anhydrous pyridine and 20 cc of acetic anhydride is heated to 60^{0}C under stirring for three hours. Then the solvent is boiled off and the obtained residue is taken up with toluene. After evaporating it the residue is crystallized from ethanol yielding 5.48 g of the compound of the title (87%). M.p. 175-177^{0}C.

Example 27: 4-(3-methyl-3H-naphtho/1,2-d/imidazol-2-yl)phenol propanoate

This compound is prepared according to the procedure

described in the foregoing example but using propionic anhydride instead of acetic anhydride. Yield 83%. M.p. 165-66°C.

Example 28: 2-(2-methoxyphenyl)-3-methyl-3H-naphtho /1,2-d/imidazole

The compound of the title is prepared by following essentially the same procedure described in example 5 but using 2-methoxy-benzaldehyde instead of 4-ethoxy-benzaldehyde. Yield 82%. M.p. 132-33°C.

Example 29: /4-(3-methyl-3H-naphtho/1,2-d/imidazol-2-yl) phenoxy/acetic acid ethyl ester.

60 cc (0.06 mole) of 1N NaOH are dripped, over a period of time of two hours, into a vigorously stirred solution of 8.22 g (0.03 mole) of the compound of example 24, 0.35 g (0.03 mole) of benzyl-tributyl ammonium chloride, and 10.4 cc (0.09 mole) of bromoacetic acid ethyl ester in 300 cc of methylene chloride. The reaction mixture is stirred for further two hours. Then 10.4 cc of bromoaceti acid ethyl ester and 60 cc of 1N NaOH are added over a period of two hours still under stirring. Stirring is prolonged for further two hours and the addition of bromoacetic acid ethyl ester and NaOH is repeated under the same conditions.

Upon filtration the unreacted starting material is recovered from the solid and purified by crystallization from dimethylformamide (3.95 g) while from the filtrate the organic layer is separated, washed with water and dried over $MgSO_4$. The solvent is then evaporated and the residue is dissolved in 50 cc or isopropanol and diluted with diethyl ether to precipitate the catalyst employed in the reaction which is filtered off. Evaporation of the solvent affords 8.6 g of a raw product which is purified by column chromatography using cyclohexane containing increasing amounts of ethyl acetate up to 8:2 as the eluting system; yield 45%. M.p. 103-4 ^{0}C (from isopropanol).

Example 30: /4-(3-methyl-3H-naphth/1,2-d/imidazol-2-yl)phenoxy/acetic acid

3.99 g (0.011 mole) of the compound of the foregoing example, 20 cc of 10% NaOH, and 40 cc of methanol are heated at the reflux temperature for about 30 minutes. Then the methanol is boiled off, the mixture is cooled to 5 ^{0}C and the pH is brought to 5 by the addition of glacial acetic acid. The solid which precipitates is recovered by filtration and crystallized from ethanol. Yield 53%. M.p. 227 ^{0}C.

Example 31: 4-(3-methyl-3H-naphth/1,2-d/imidazol-2-yl)--N,N,2,6-tetramethylbenzenamine

The compound of the title is prepared by following essentially the same procedures described in example 5 but using 3,5-dimethyl-4-dimethylamino-benzaldehyde instead of 4-ethoxybenzaldehyde.

Purification of the raw product is achieved by triturating the residue with light petroleum, filtering it and crystallizing the obtained product from cyclohexane first and then from ethanol/water. Yield 40%. M.p. 136-7^{0}C.

Example 32: 3-(1-methylethyl)-2-(4-methyoxyphenyl)-3H--naphth/1,2-d/imidazole

In a multi-necked 500 cc flask equipped with a mechanical stirrer and a Dean-Stark apparatus a solution of 2 g (0.01 mole) of N^2-(1-methylethyl)naphthalendiamine (known from J. Org. Chem. 37 (22), 3566 (1972)), 1.36 g (0.01 mole) of 4-methoxybenzaldehyde and 300 cc of toluene are heated at the reflux temperature under argon atmosphere for 3 hours. Then 2 g of 5% Palladium on carbon are added and the reaction mixture is heated at the reflux temperature for further three hours. Upon filtering off the catalyst, the filtrate is taken to small volume yielding 2.86 g of a raw product which is recovered by filtration and purified by crystallization from ethyl acetate. From the mother liquors taken to dryness further 1.7 g are obtained which are chromatographed through a silicagel column eluting with benzene: ethyl acetate 95:5. Overall yield 57%. M.p. 162-63^{0}C.

The compound of the title is also prepared by following the same procedure described in example 5 but starting from N-isopropyl-1-nitroso-2-naphthaleneamine instead of N-methyl-1-nitroso-2-naphthaleneamine and using 4-methoxybenzaldehyde instead of 4-ethoxybenzaldehyde. Yield 60%. M.p. 162-63^{0}C (from ethyl acetate).

The starting N-isopropyl-1-nitroso-2-naphthaleneamine is prepared through reaction of 1-nitroso-2-naphthol with isopropylamine according to the method described in J. Am. Chem. Soc. 70, 2415 (1948).

Example 33: 3-butyl-2-(4-methoxyphenyl)-3H-naphtho[1,2-d]imidazole.

The compound of the title is prepared by following essentially the same procedure described in example 5 but starting from 2-butylamino-1-nitrosonaphthalene instead of 2-methylamino-1-nitrosonaphthalene and employing 4-methoxybenzaldehyde instead of 4-ethoxybenzaldehyde. Yield 53%. M.p. 99,5-100,5 ^{0}C.

Example 34: 8-methoxy-2-(4-methoxyphenyl)-3-methyl-3H-naphtho[1,2-d]imidazole hydrochloride

The compound of the title, as the free base, is prepared by following essentially the same procedure described in example 5 but using 7-methoxy-2-methylamino-1-nitroso-naphthalene instead of 2-methylamino-1-nitrosonaphthalene and 4-methoxybenzaldehyde instead of 4-ethoxybenzaldehyde. By addition of HCl to a diethyl ether solution of the free base, the corresponding hydrochloride precipitates. Yield 40%. M.p. 265 ^{0}C dec. (from methanol).

Example 35: 7-methoxy-2-(4-methoxyphenyl)-3-methyl-3H-naphtho[1,2-d]imidazole hydrochloride

The compound of the title is prepared by following essentially the same procedure described in the foregoing example but starting from 6-methoxy-2-methylamino-1-nitrosonaphthalene instead of 7-methoxy-2-methylamino-1-nitrosonaphthalene. Yield 35%. M.p. 261 ^{0}C (from methanol). The starting 6-methoxy-2-methylamino-1-nitrosonaphthalene is prepared by adding 3.75 g of 6-methoxy-1-nitroso-2-naphthol to a solution of 9.5 cc of 35% CH_3NH_2 in 15 cc of water cooled to about 10 ^{0}C, heating the reaction mixture to 40 ^{0}C for a few minutes and finally recovering the solid which precipitates on cooling to room temperature.

Example 36: 6-chloro-7-methoxy-2-(4-methoxyphenyl)-3-methyl-3H-naphth/1,2-d/imidazole

The compound of the title is prepared by following essentially the same procedure described in example 5 but starting from 5-chloro-6-methoxy-2-methylamino-1-nitrosonaphthalene instead of 2-methylamino-1-nitrosonaphthalene and employing 4-methoxybenzaldehyde instead of 4-ethoxybenzaldehyde. Yield 48%. M.p. 247-48 ^{0}C (from ethanol). The starting 5-chloro-6-methoxy-2-methylamino-1-nitrosonaphthalene is prepared through reaction of methylamine with 5-chloro-6-methoxy-1-nitroso-2-naphthol following the procedure described in the second portion of the foregoing example. In its turn this last compound is prepared by nitrosation of 5-chloro-6-methoxy-2-naphthol obtained from (5-chloro-6-methoxy-2-naphthalenyl)-ethanone which is a commercial product.

Example 37: 3-cyclohexyl-2-(4-methoxyphenyl)-3H-naphth[1,2-d]imidazole hydrochloride

The compound of the title is prepared by following essentially the same procedure described in example 34 but using 2-cyclohexylamine-1-nitrosonaphthalene instead of 7-methoxy-2-methylamino-1-nitrosonaphthalene. Yield 76%. M.p. 238°C dec.

The starting 2-cyclohexylamine-1-nitrosonaphthalene is prepared by reacting 1-nitroso-2-naphthol with cyclohexylamine according to the procedure described in the second part of example 35.

Example 38: 3-ethyl-2-(4-methoxyphenyl)-3H-naphtho[1,2-d]imidazole

The compound of the title is prepared according to the procedure described in example 5 but starting from 2-ethylamino-1-nitrosonaphthalene instead of 2-methylamino-1-nitrosonaphthalene and adding 4-methoxybenzaldehyde instead of 4-ethoxybenzaldehyde. Yield 81%. M.p. 144-146°C (from ethyl acetate).

The starting 2-ethylamino-1-nitrosonaphthalene is prepared by reacting 1-nitroso-2-naphthol with ethylamine following the same procedure described in the second part of example 35.

By operating according the procedures of the foregoing examples the following compounds may be prepared:

3-(1-ethylpropyl)-2-(4-methoxyphenyl)-3H-naphtho[1,2-d]imidazole

3-cyclobutyl-2-(4-methoxyphenyl)-3H-naphtho[1,2-d]imidazole

3-cyclopropyl-2-(4-methoxyphenyl)-3H-naphtho[1,2-d]imidazol

3-cyclopentyl-2-(4-methoxyphenyl)-3H-naphtho[1,2-d]imidazol

3-cyclohepyl-2-(4-methoxyphenyl)-3H-naphtho[1,2-d]imidazole

3-(2-propenyl)-2-(4-methoxyphenyl)-3H-naphtho[1,2-d]imidazole

3-(1,1-dimethylethyl)-2-(4-methoxyphenyl)-3H-naphtho[1,2-d]imidazole

3-(1-methylpropyl)-2-(4-methoxyphenyl)-3H-naphtho[1,2-d]imidazole

3-(1-ethylpropyl)-2-(4-methoxyphenyl)-3H-naphtho[1,2-d]imidazole

3-(1-methyl-2-propenyl)-2-(4-methoxyphenyl)-3H-naphtho[1,2-d]imidazole

3-(2-propynyl)-2-(4-methoxyphenyl)-3H-naphtho[1,2-d]imidazole

6-chloro-3-methyl-2-phenyl-3H-naphtho[1,2-d]imidazole

3-ethyl-7,8-dimethoxy-2-phenyl-3H-naphtho[1,2-d]imidazole

7-chloro-3-methyl-2-phenyl-3H-naphtho[1,2-d]imidazole

8-chloro-3-methyl-2-phenyl-3H-naphtho[1,2-d]imidazole

7-methoxy-3-methyl-2-phenyl-3H-naphtho[1,2-d]imidazole

8,9-dichloro-3-ethyl-2-phenyl-3H-naphtho[1,2-d]imidazole

3-ethyl-2-phenyl-3H-naphtho[1,2-d]imidazole

2-phenyl-3-propyl-3H-naphtho[1,2-d]imidazole

3-(1-methylethyl)-2-phenyl-3H-naphtho[1,2-d]imidazole

3-butyl-2-phenyl-3H-naphtho[1,2-d]imidazole

2-(3,4-dimethoxyphenyl)-3-methyl-3H-naphtho[1,2-d]imidazol

3-ethyl-2-(3-methoxyphenyl)-3H-naphtho[1,2-d]imidazole

2-(4-fluorophenyl)-3-methyl-3H-naphtho[1,2-d]imidazole

3-methyl-2-[4-(1-methylethyl)phenyl]-3H-naphtho[1,2-d]imidazole

3-methyl-2-(3-methylphenyl)-3H-naphtho[1,2-d]imidazole

3-methyl-2-[4-(2-propenyloxy)phenyl]-3H-naphtho[1,2-d]imidazole

3-methyl-2-[4-(2-methyl-2-propenyloxy)phenyl]-3H-naphtho[1,2-d]imidazole

3-methyl-2-[4-(2-propynyloxy)phenyl]-3H-naphtho[1,2-d]imidazole

3-methyl-2-[3-(2-propynyloxy)phenyl)-3H-naphtho[1,2-d]imidazole

3-methyl-2-(3,4-dimethylphenyl)-3H-naphtho[1,2-d]imidazole

2-(4-chlorophenyl)-3-ethyl-3H-naphtho[1,2-d]imidazole

3-ethyl-2-(2-thienyl)-3H-naphtho[1,2-d]imidazole

3-methyl-2-(5-methyl-2-thienyl)-3H-naphtho[1,2-d]imidazole

7,8-dimethoxy-3-methyl-2-(2-thienyl)-3H-naphtho[1,2-d]imidazole

3-methyl-2-(5-phenyl-2-thienyl)-3H-naphtho[1,2-d]imidazole

2-(2-imidazolyl)-3-methyl-3H-naphtho[1,2-d]imidazole

3-methyl-2-pyrazinyl-3H-naphtho[1,2-d]imidazole

3-methyl-2-(3-pyridazinyl)-3H-naphtho[1,2-d]imidazole

3-methyl-2-(6-phenyl-2-pyridyl)-3H-naphtho[1,2-d]imidazole

3-ethyl-2-(6-methyl-2-pyridyl)-3H-naphtho[1,2-d]imidazole

3-methyl-2-(1-methyl-pyrrol-3-yl)-3H-naphtho[1,2-d]imidazole

2-(3-isoxazolyl)-3-methyl-3H-naphtho[1,2-d]imidazole

N,N-dimethyl-4-(3-ethyl-3H-naphtho[1,2-d]imidazol-2-yl)benzenamine

2-(3-chloro-4-methoxyphenyl)-3-methyl-3H-naphtho[1,2-d]imidazole

2-(3-methyl-4-methoxyphenyl)-3-ethyl-3H-naphtho[1,2-d]imidazole

N,N-di(1-methylethyl)-4-(3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)benzenamine

N-[4-(3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)phenyl]propionamide

N-[4-(3-ethyl-3H-naphtho[1,2-d]imidazol-2-yl)phenyl]acetamide

N-methyl-4-(3-ethyl-3H-naphtho[1,2-d]imidazol-2-yl)benzenamine

N-(1-methylethyl)-4-(3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)benzeneamine

N-methyl-4-(7-methoxy-3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)-benzenamine

4-methoxy-2-(4-methoxyphenyl)-3-methyl-3H-naphtho[1,2-d]imidazole

5-methoxy-2-(4-methoxyphenyl)-3-methyl-3H-naphtho[1,2-d]imidazole

6-methoxy-2-(4-methoxyphenyl)-3-methyl-3H-naphtho[1,2-d]imidazole

9-methoxy-2-(4-methoxyphenyl)-3-methyl-3H-naphtho[1,2-d]imidazole

3-ethyl-7-methoxy-2-(4-methoxyphenyl)-3H-naphtho[1,2-d]imidazole

3-butyl-7-methoxy-2-(4-methoxyphenyl)-3H-naphtho[1,2-d]imidazole

2-(4-methoxyphenyl)-3-methyl-7-methylthio-3H-naphtho[1,2-d]imidazole

7-ethylthio-3-methyl-2-phenyl-3H-naphtho[1,2-d]imidazole

2-(4-methoxyphenyl)-3,7-dimethyl-3H-naphtho[1,2-d]imidazole

7-chloro-2-(4-methoxyphenyl)-3-methyl-3H-naphtho[1,2-d]imidazole

7-ethoxy-2-(4-methoxyphenyl)-3-methyl-3H-naphtho[1,2-d]imidazole

7-ethyl-2-(4-methoxyphenyl)-3-methyl-3H-naphtho[1,2-d]imidazole

2-(4-methoxyphenyl)-3-methyl-7-(1-methylethyl)-3H-naphtho[1,2-d]imidazole

7-trifluoromethoxy-2-(4-methoxyphenyl)-3-methyl-3H-naphtho[1,2-d]imidazole

6-chloro-7-methoxy-3-methyl-2-phenyl-3H-naphtho[1,2-d]imidazole

6-chloro-3-ethyl-7-methoxy-2-(4-methoxyphenyl)-3H-naphtho[1,2-d]imidazole

4-(7-methoxy-3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)-2,N,N-trimethylbenzenamine

4-(7,8-dimethoxy-3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)-2,N,N-trimethylbenzenamine

4-(3-ethyl-7-methoxy-3H-naphtho[1,2-d]imidazol-2-yl)-2,N,N-trimethylbenzenamine

4-(7-methoxy-3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)-2,6,N,N-tetramethylbenzenamine

N-ethyl-N-methyl-4-(3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)benzenamine

N-methyl-N-(1-methylethyl)-4-(3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)benzeneamine

N-methyl-4-(3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)-N-propylbenzenamine

2,N-dimethyl-4-(7-methoxy-3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)-N-propylbenzenamine

3-methyl-2-[4-(1-pyrrolidinyl)phenyl]-3H-naphtho[1,2-d]imidazole

3-methyl-2-[3-methyl-4-(1-pyrrolidinyl)phenyl]-3H-naphtho[1,2-d]imidazole

7-methoxy-3-methyl-2-[4-(1-piperidyl)phenyl]-3H-naphtho[1,2-d]imidazole

7,8-dimethoxy-3-methyl-2-[4-(4-methyl-1-piperazinyl)phenyl]-3H-naphtho[1,2-d]imidazole

3-methyl-2-[3-methyl-4-(4-methyl-1-piperazinyl)phenyl]--3H-naphtho[1,2-d]imidazole

3-ethyl-2-[3-methyl-4-(1-piperazinyl)phenyl]-3H-naphtho[1,2-d]imidazole

7-methoxy-3-methyl-2-[4-(4-morpholinyl)phenyl]-3H-naphtho[1,2-d]imidazole

7-methoxy-2-(2-methoxyphenyl)-3-methyl-3H-naphtho[1,2--d]imidazole

2-(2-acetyloxyphenyl)-3-methyl-3H-naphtho[1,2-d]imidazole

2-(4-acetyloxyphenyl)-7-methoxy-3-methyl-3H-naphtho[1,2--d]imidazole

2-(4-carboxy-methoxyphenyl)-7-methoxy-3-methyl-3H--naphtho[1,2-d]imidazole

Example 39

A tablet is prepared from

2-(4-methoxyphenyl)-3-(1-methylethyl)-3H-naphth[1,2-d]imidazole	500 mg
starch	40 mg
talc	10 mg
magnesium stearate	10 mg

Example 40

A tablet is prepared from

2-(4-methoxyphenyl)-3-methyl-3H-naphth[1,2-d]imidazole	300 mg
lactose	50 mg
microcrystalline cellulose	50 mg
stearic acid	10 mg
colloidal silica	5 mg

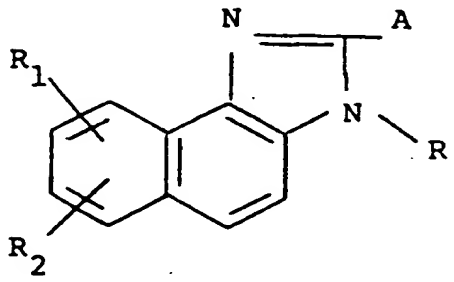
Example 41

A capsule is prepared from

4-(3-methyl-3H-naphth[1,2-d]imidazol-2-yl)-2,N,N-trimethylbenzenamine	400 mg
talc	40 mg
sodium carboxymethylcellulose	40 mg
starch	120 mg

Claims for all designated countries except Austria

1) A novel 3H-naphtho[1,2-d]imidazole derivative having the following general formula



wherein R stands for (C_{1-6})alkyl, (C_{3-6})alkenyl, (C_{3-6})alkynyl or (C_{3-7})cycloalkyl, R_1 and R_2 each independently may represent hydrogen, halogen, (C_{1-4})alkyl, (C_{1-4})alkylthio, (C_{1-4})alkoxy or halo(C_{1-4})alkoxy and the symbol A represents a 5- or 6-membered heteroaromatic ring which may contain one or two heteroatoms independently selected from oxygen, nitrogen and sulfur and may be optionally substituted with (C_{1-4})alkyl or phenyl groups or it may represent a phenyl radical optionally substituted with one to three groups independently selected from halogen, (C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{3-4})alkenyloxy, (C_{3-4})alkynyloxy, hydroxy, benzyloxy, (C_{2-4})alkanoyloxy, carboxy-methoxy, [carbo(C_{1-4})alkoxy]methoxy, methylenedioxy, amino, mono- and di-(C_{1-4})alkylamino, (C_{2-4})alkanoylamino, benzoylamino and a heterocyclic radical derived from pyrrolidine, piperidine, piperazine, (C_{1-4})alkylpiperazine and morpholine; with the proviso that when simultaneously R represents a methyl group and R_1 and R_2 are both hydrogen, A cannot represent a 2-hydroxyphenyl group and

with the further proviso that when simultaneously R stands for an ethyl radical, one of R_1 and R_2 is hydrogen and the other one is a methoxy group, A cannot be a 4-dimethylaminophenyl group; and salts therewith of pharmaceutically acceptable acids.

2) A compound as in claim 1 wherein R stands for (C_{1-6})alkyl, (C_{3-6})alkenyl, (C_{3-6})alkynyl or (C_{3-7})cycloalkyl, R_1 and R_2 each independently represent hydrogen, halogen or (C_{1-4})alkoxy and the symbol A represents a phenyl radical optionally substituted with one to three groups independently selected from halogen, (C_{1-4})alkyl, (C_{1-4})alkoxy, hydroxy, benzyloxy, (C_{2-4})alkanoyloxy, carboxy-methoxy, /carbo(C_{1-4})alkoxy/methoxy, methylenedioxy, amino, mono- and di-(C_{1-4})alkylamino, (C_{2-4})alkanoylamino and benzoylamino; with the proviso that when R represents methyl and R_1 and R_2 are both hydrogen, A cannot represent a 2-hydroxyphenyl group, and with the further proviso that when simultaneously R stands for ethyl, one of R_1 and R_2 is hydrogen and the other is a methoxy group, A cannot represent a 4-dimethylaminophenyl group; and salts therewith of pharmaceutically acceptable acids.

3) A compound as in claim 1 wherein R stands for (C_{1-6})alkyl, R_1 and R_2 are hydrogen, and the symbol A represents a heteroaromatic ring selected from furyl, thienyl, pyrrolyl and pyridyl, optionally substituted by (C_{1-4})alkyl groups; and salts therewith of pharmaceutically acceptable acids.

4) A compound as in claim 1 wherein R stands for (C_{1-6})alkyl, R_1 and R_2 are both hydrogen and the symbol A represents a phenyl radical optionally substituted with one to three groups independently selected from (C_{1-4})alkyl, (C_{1-4})alkoxy, amino, mono- and di-(C_{1-4})alkylamino; and salts therewith of pharmaceutically acceptable acids.

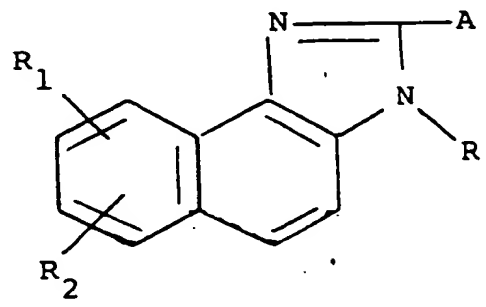
5) A compound of claim 1 which is 2-(4-methoxyphenyl)-3--(1-methylethyl)-3H-naphth[1,2-d]imidazole.

6) A compound of claim 1 which is 2-(4-methoxyphenyl)-3--methyl-3H-naphth[1,2-d]imidazole

7) A compound of claim 1 which is 4-(3-methyl-3H--naphth[1,2-d]imidazol-2-yl)-2,N,N-trimethylbenzenamine.

8) Use of the compounds of claim 1 as antiinflammatory agents.

9) A composition suitable for antiinflammatory use which comprises from about 50 to about 1000 mg of a compound of formula I



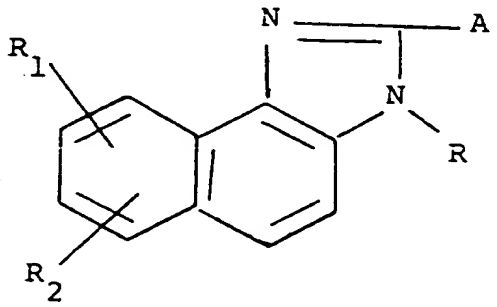
I

wherein R, R_1, R_2 and the symbol A are as defined in claim 1 or a salt therewith of pharmaceutically acceptable acids, in admixture with a pharmaceutical carrier.

10) Use of the compounds of claim 1 as antimicrobial agents.

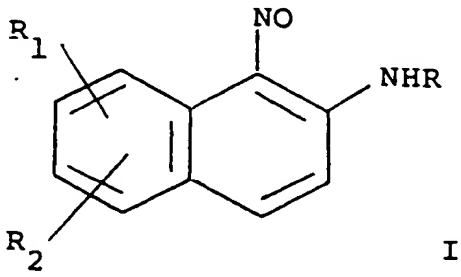
11) A composition suitable for antimicrobial use which comprises from about 0.1 percent by weight to about 10 percent by weight of a compound of claim 1.

12) A process for preparing a compound of formula I



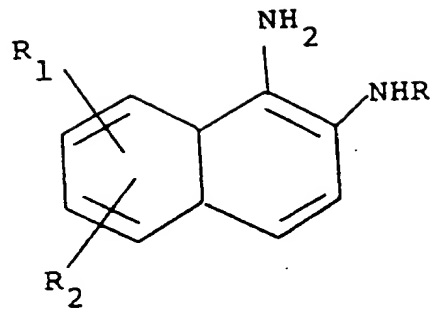
I

wherein R, R_1, R_2 and A are as defined in claim 1 characterized in that a N-substituted-1-nitroso-2-naphthaleneamine derivative of formula IV



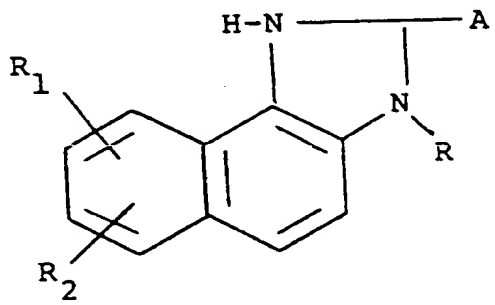
IV

wherein R, R_1 and R_2 are as defined in claim 1, is reduced to the corresponding N^2-substituted-naphthalen-1,2-diamine of formula II



II

by means of hydrogen in the presence of a hydrogenation catalyst, said intermediate compound is condensed with a suitably selected aldehyde of formula ACHO wherein A is as defined in claim 1, to yield the corresponding imidazoline derivative of formula III



III

which in its turn is transformed into the final compound of formula I by means of a dehydrogenating agent; said process being further characterized in that

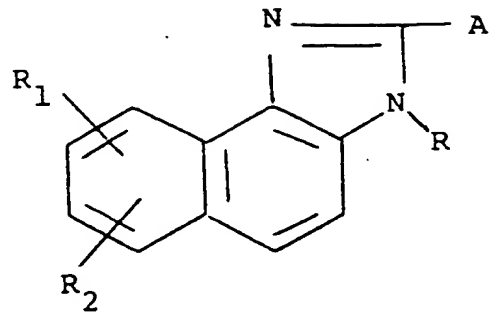
a) when a compound of formula I is obtained wherein A stands for a hydroxyphenyl radical, it may be transformed into the corresponding compound of formula I wherein A is phenyl substituted with (C_{1-4})alkoxy, (C_{3-4})alkenyloxy, (C_{3-4})alkynyloxy, benzyloxy, (C_{2-4})alkanoyloxy, carboxy-methoxy or carbo(C_{1-4})alkoxymethoxy, by reaction with suitably agents such as (C_{1-4})alkyl, (C_{3-4})alkenyl, (C_{2-4})alkynyl and benzyl halogenides, tosylates or mesylates,

(C_{2-4})alkanoyl, halogenides or anhydrides, an α-haloacetic acid and its (C_{1-4})alkyl esters, and

b) when a compound of formula I is obtained wherein A is phenyl substituted with alkanoylamino or benzoylamino groups, it may be converted into the corresponding compound of formula I wherein A is phenyl substituted with amino by acid hydrolysis, or it may be transformed into the corresponding compound of formula I wherein A is phenyl substituted with mono-(C_{1-4})alkylamino groups by reaction with alkyl halogenides followed by alkaline hydrolysis.

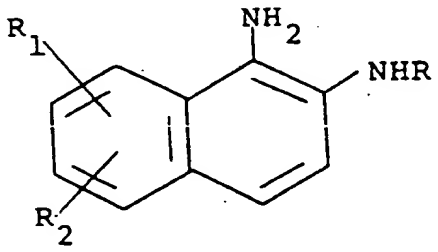
CLAIMS for Austria

1) A process for preparing a compound of formula I



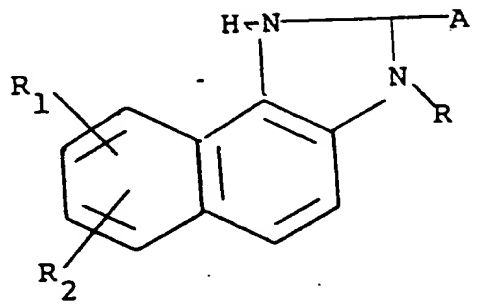
I

wherein R, R_1, R_2 and A are as defined in claim 1 characterized in that a N^2-substituted-naphthalen-1,2-diamine of formula II



II

wherein R, R_1 and R_2 are as defined in claim 1, is condensed with a suitably selected aldehyde of formula ACHO wherein A is as defined in claim 1, to yield the corresponding imidazoline derivative of formula III



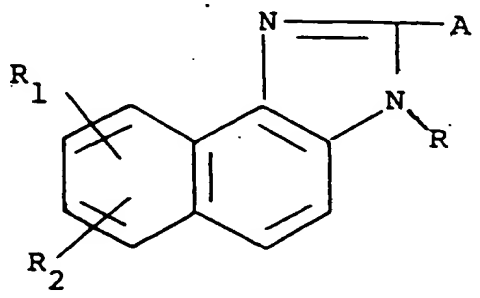
III

which in its turn is transformed into the final compound of formula I by means of a mild oxidizing agent or a dehydrogenating agent; said process being further characterized in that

a) when a compound of formula I is obtained wherein A stands for a hydroxyphenyl radical, it may be transformed into the corresponding compound of formula I wherein A is phenyl substituted with (C_{1-4})alkoxy, (C_{3-4})alkenyloxy, (C_{3-4})alkynyloxy, benzyloxy, (C_{2-4})alkanoyloxy, carboxy-methoxy or /carbo(C_{1-4})alkoxy/methoxy, by reaction with suitable agents such as (C_{1-4})alkyl, (C_{3-4})alkenyl, (C_{3-4})alkynyl and benzyl halogenides, tosylates or mesylates, (C_{2-4})alkanoyl halogenides or anhydrides, an α-haloacetic acid and its (C_{1-4})alkyl esters, and

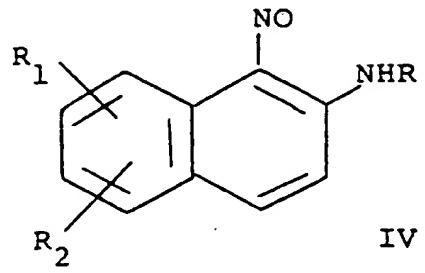
b) when a compound of formula I is obtained wherein A is phenyl substituted with alkanoylamino or benzoylamino groups, it may be converted into the corresponding compound of formula I wherein A is phenyl substituted with amino by acid hydrolysis, or it may be transformed into the corresponding compound of formula I wherein A is phenyl substituted with mono-(C_{1-4})alkylamino groups by reaction with alkyl halogenides followed by alkaline hydrolysis.

2) A process for preparing a compound of formula I



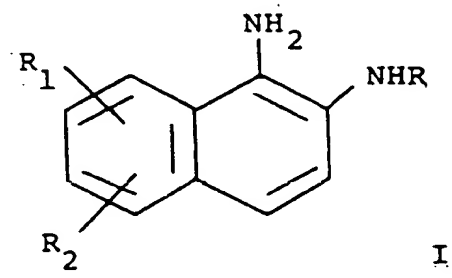
I

wherein R, R_1, R_2 and A are as defined in claim 1 characterized in that a N-substituted-1-nitroso-2-naphthaleneamine derivative of formula IV



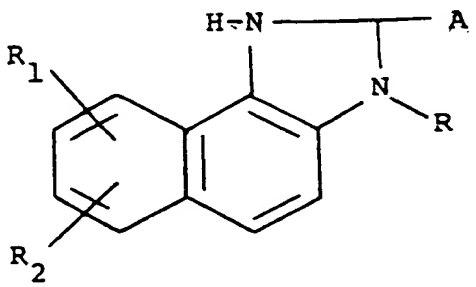
IV

wherein R, R_1 and R_2 are as defined in claim 1, is reduced to the corresponding N^2-substituted-naphthalen--1,2-diamine of formula II



II

by means of hydrogen in the presence of a hydrogenation catalyst, said intermediate compound is condensed with a suitably selected aldehyde of formula ACHO wherein A is as defined in claim 1, to yield the corresponding imidazoline derivative of formula III



III

which in its turn is transformed into the final compound of formula I by means of a dehydrogenating agent; said process being further characterized in that:

a) when a compound of formula I is obtained wherein A stands for a hydroxyphenyl radical, it may be transformed into the corresponding compound of formula I wherein A is phenyl substituted with (C_{1-4})alkoxy, (C_{3-4})alkenyloxy, (C_{3-4})alkynyloxy, benzyloxy, (C_{2-4})alkanoyloxy, carboxy-methoxy or /carbo(C_{1-4})alkoxy/methoxy, by reaction with suitably agents such as (C_{1-4})alkyl, (C_{3-4})alkenyl, (C_{3-4})alkynyl and benzyl halogenides, tosylates or mesylates, (C_{2-4})alkanoyl halogenides or anhydrides, an α-haloacetic acid and its (C_{1-4})alkyl esters, and

b) when a compound of formula I is obtained wherein A is phenyl substituted with alkanoylamino or benzoylamino groups, it may be converted into the corresponding compound of formula I wherein A is phenyl substituted with amino by acid hydrolysis, or it may be transformed into the corresponding compound of formula I wherein A is phenyl substituted with mono-(C_{1-4})alkylamino groups by reaction with alkyl halogenides followed by alkaline hydrolysis.

3) The process of claim 9 wherein the intermediates of formula II and III are not isolated from the reaction medium.

4) A process for preparing a compound of formula I

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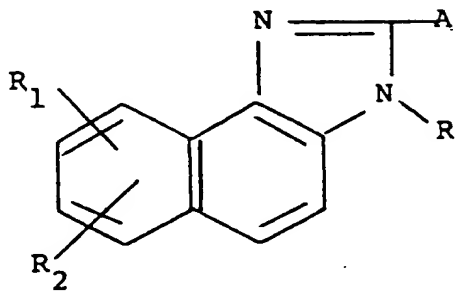
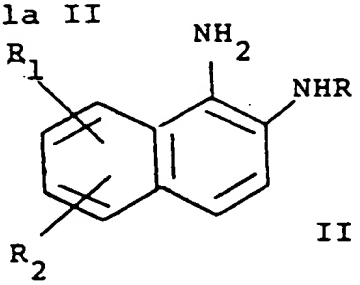


I

wherein R, R_1, R_2 and A are as defined in claim 1, characterized in that a N^2-substituted naphthalen-1,2--diamine of formula II

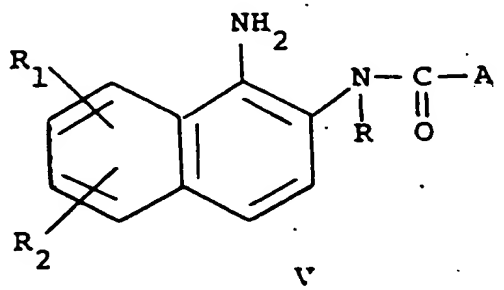


II

wherein R, R_1 and R_2 are as defined in claim 1, is condensed with an acid derivative of formula A-C(=O)-X wherein A is as defined in claim 1 and X may represent

- a chlorine atom
- a group $-OR_3$ wherein R_3 may be the same radical -C(=O)-A, a trifluoroacetyl, ethoxycarbonyl or alkylsulphonyl moiety, or
- a group $-OR_4$ wherein R_4 stands for methyl or ethyl,

to yield the corresponding mono-acylated compound of formula V



V

which in its turn is cyclized to the final compound of formula I; said process being further characterized in that

a) when a compound of formula I is obtained wherein A stands for a hydroxyphenyl radical, it may be transformed into the corresponding compound of formula I wherein A is phenyl substituted with (C_{1-4})alkoxy, (C_{3-4})alkenyloxy, (C_{3-4})alkynyloxy, benzyloxy, (C_{2-4})alkanoyloxy, carboxy-methoxy or [carbo(C_{1-4})alkoxy]methoxy, by reaction with suitable agents such as (C_{1-4})alkyl, (C_{3-4})alkenyl, (C_{3-4})alkynyl, and benzyl halogenides, tosylates or mesylates, (C_{2-4})alkanoyl halogenides or anhydrides, an α-haloacetic acid and its (C_{1-4})alkyl esters and

b) when a compound of formula I is obtained wherein A is phenyl substituted with alkanoylamino or benzoylamino groups, it may be converted into the corresponding compound of formula I wherein A is phenyl substituted with amino by acid hydrolysis, or it may be transformed into the corresponding compound of formula I wherein A is phenyl substituted with mono-(C_{1-4})alkylamino groups by reaction with alkyl halogenides followed by alkaline hydrolysis.

5) A process according to any of the preceeding claims for preparing 2-(4-methoxyphenyl)-3-(1-methylethyl)-3H-naphtho[1,2-d]imidazole

6) A process according to any of claims 1, 2, 3 and 4 for preparing 2-(4-methoxyphenyl)-3-methyl-3H-naphtho[1,2-d]imidazole

7) A process according to any of claims 1, 2, 3 and 4 for preparing 4-(3-methyl-3H-naphtho[1,2-d]imidazol-2-yl)-2,N,N-trimethylbenzenamine.

European Patent Office

0012866

Application number

EP 79 10 4750

EUROPEAN SEARCH REPORT

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
D	DE - B - 1 137 625 (KALLE) * Columns 1-3,8; column 16, example 14; column 17 *	1,2,5-7
A	GB - A - 1 484 615 (GRUPPO LEPETIT) * Pages 1-5,9; page 11, examples 1,2 *	1,2,5-7

CLASSIFICATION OF THE APPLICATION (Int Cl.)

C 07 D 235/02
401/04
401/10
403/04
405/04
405/10
409/04
413/04
413/10
A 61 K 31/33

TECHNICAL FIELDS SEARCHED (Int.Cl.)

C 07 D 235/02
401/04
401/10
403/04
405/04
405/10
409/04
413/04
413/10
A 61 K 31/33

CATEGORY OF CITED DOCUMENTS

X. particularly relevant
A technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

& member of the same patent family, corresponding document

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	15-04-1980	DE BUYSER